for tachyplesin I. Since the random-coiled magainin 2 can be more completely covered by PEGs than does the β-sheet tachyplesin I, the PEGylation effect on the decreased binding is larger for magainin 2, showing the dependence of PEGylation on the peptide structure. These results qualitatively support that PEGylated magainin 2 and tachyplesin I have the different extents of the membrane-permeabilizing activity on lipid bilayer surface.

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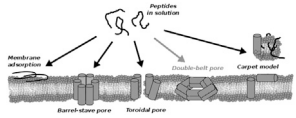
Double-Belt a Novel Structure of Membrane Pore

Robert Vacha[1], Daan Frenkel[2].
[1]Masaryk University, Brno, Czech Republic, [2]University of Cambridge, Cambridge, United Kingdom.

Amphiphilic proteins and peptides can induce formation of stable and metastable pores in phospholipid membranes, which has been associated with toxicity or antimicrobial activity. Using coarse-grained simulations we have studied peptide orientation within the pores and have found that peptides can be oriented perpendicular, parallel, or tilted with respect to the membrane plane. The orientation depends on the length of the peptide and its hydrophobicity distribution, which we rationalized in terms of the hydrophobic mismatch. Apart from well-known barrel-stave or toroidal pores our simulations suggest a novel 'double-belt' pore structure, where peptides within the membrane pore are oriented parallel to the membrane plane. This result was verified using more detailed simulations with the MARTINI force field, where the double-belt structure was stable in microsecond time scale of our simulation.



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Interaction of the Inward Rectifier Potassium Channel Kir 2.2 with Phosphatidylserine

Mercedes Alfonso Prieto, Lucie Delemotte, Michael L. Klein.
Institute for Computational Molecular Science, Temple University, Philadelphia, PA, USA.

Inward-rectifier K^+ (Kir) channels are ion channels that transport potassium into the cell. They are essential to maintain the resting membrane potential and to regulate the action potential duration in excitable cells *[1]*. As a consequence, Kir mutations result in several diseases, such as periodic paralysis or cardiac arrhythmia *[1, 2]*.

The activity of Kir channels is regulated by phosphatidylinositol-(4,5)-bisphosphate (PIP_2), a negatively charged phospholipid that has been recognized as one of the major regulators of membrane excitability *[2]*. Moreover, it has been suggested that Kir activation is not only regulated by PIP_2, but it has a secondary, non-specific requirement for other anionic phospholipids *[3]*.

Here we have investigated the interaction of phosphatidylserine (PS) with Kir 2.2 by means of all-atom molecular dynamics (MD). Simulations have been performed on both the apo and PIP_2-bound states of the channel *[4]*, embedded in a POPS membrane in the presence of KCl. These trajectories reveal the key protein residues interacting with POPS, complementing previous docking *[3]* and coarse-grain *[5]* studies. Furthermore, they suggest that the Kir 2.2-POPS interactions drive the cytoplasmic domain closer to the membrane and help to pre-assemble the PIP_2 binding site. In other words, our simulations provide a molecular picture of the sensitized state proposed by Nichols and coworkers to explain the synergistic effect of anionic phospholipids *[3]*.

[1] Physiol. Rev. 90:291-366 (2010).
[2] Pflugers Arch. 460:321-341 (2010).
[3] (a) Biophys. J. 100:620-628 (2011). (b) J. Biol. Chem. 288:16726-16737 (2013). (c) Biophys. J., 104:433a (2013).
[4] (a) Science, 326:1668-1674 (2009). (b) Nature (Letter), 477:495-499 (2011)
[5] Biochemistry, 52:279-281 (2013).

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Permeation of Lipidated Protein in Bilayer using Unbiased Simulations Reveals Signature Motif for Protein-Membrane Binding

Lipi Thukral[1], Durba Sengupta[2], Rajesh S. Gokhale[1].
[1]CSIR- Institute of Genomics and Integrative Biology, New Delhi, India, [2]CSIR- National chemical laboratory, Pune, India.

Structural and dynamic reorganization of membrane domains by proteins is a central theme in many biological processes. Eukaryotic cells possess potential regulatory mechanisms to mediate many of its protein-membrane interactions in form of lipid-modified proteins. Two forms of these proteins exist; cytosolic conformers and functional membrane bound complexes. At present, there are many questions that remain to be answered with regard to the molecular mechanism of interaction of lipidated proteins with membrane that generates a trigger for physiological response, only upon membrane binding.

A particularly exciting area of membrane trafficking, autophagy, has been receiving increasing attention. It is a cellular degradative process that involves the formation of autophagosome, a specialized vesicle to deliver the dispensable cellular cargo to the lysosome. During initiation of autophagy, key regulator protein, LC3-I (cytosolic form) is conjugated reversibly to phosphotidylethanolamine (PE) resulting in a nonsoluble form of LC3 that stably associates with the autophagosomal membrane. The present work reports partitioning of PE chain of LC3 in bilayer using MARTINI force field based coarse grain molecular dynamics simulations.

Spontaneous insertion of PE chain at microseconds timescale is observed in fourteen out of fifteen trajectories. This unbiased insertion of lipidated protein reveals a novel insertion pathway through an arginine rich patch that drives the insertion of PE chain. Interestingly, membrane curvature properties reveal variations in spontaneous curvature of the membrane, confirming the role of LC3 in forming a vesicle during autophagy. This first unbiased study of active insertion of a lipid chain provides future avenues to investigate detailed regulatory aspects of this phenomenon using experimental techniques.

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Structural Basis of Lipid Exchange in the Oxysterol-Binding Protein Homologue (OSH) Family

Stefano Vanni, Joachim Moser, von Filseck, Bruno Mesmin, Bruno Antonny, Guillaume Drin.
Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, Valbonne, France.

Oxysterol-binding proteins, long known to be involved in the non-vesicular transport of sterol, have recently been shown to also transfer glycerophospholipids, such as phosphatidyl-inositol-4-phosphate (PI4P) and phosphatidylserine (PS) between membranes.

Using a combination of atomistic molecular dynamics simulations and in vitro lipid transport assays, we characterized the structural determinants that regulate the extraction and release of different lipids by the various Osh proteins.

Our results define how distinct lipid-binding modes govern the ability of Osh proteins to transport or exchange lipids between organelles.

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Study of the Mecanism of Action of a Hybrid Peptide in POPG:POPC Bilayers

Gabriel C. Da Hora, Thereza Amélia Soares.
Departament of Fundamental Chemistry, Federal University of Pernambuco, Recife - Pernambuco, Brazil.

A hybrid peptide sequence has been synthesized from the antimicrobial peptides pediocin A and plantaricin 149A. Previous studies of circular dichroism and fluorescence spectroscopic studies have shown a disordered to ordered conformational transition of the peptide upon binding to POPG but not to POPC. Further, single vesicle experiments under optical microscopy observation have indicated that at low concentrations the peptide causes the disruption of POPG membrane and formation of small, heterogeneous complexes of phospholipids and peptides. In order to analyze those interactions, concentration effects and to propose a disruption mechanism, molecular dynamics simulations were carried out using the GROMOS parameter set 54A7 and MARTINI. The systems were analyzed with respect to time-dependent (peptide secondary structure and lipid tilt angle), and average properties (density profiles and deuterium order parameters).

It was found that the peptides adsorb on both PG and PC membranes via electrostatic interactions. Only upon binding to the PG surface there is an increase of helical content compared to the peptide in solution. Higher helical content is also observed for the single peptide embedded in PG compared to PC membranes. The density of the membrane medium makes conformational transition of the peptide embedded slower than on the surface of the membrane. Our simulations indicate disruption of the membrane without deep penetration of the peptides. Evidence for that comes from increased disorder of the membrane and persistent interactions between the peptide and membrane headgroups throughout the membrane disruption process. Our findings suggest that the hybrid peptide disrupt the membrane via a carpet-like mechanism which has also been postulated for the action of Pediocin A and Plantaricin 149A [1,2].

[1] Gaussier et al. App. Environm. MicroBiol, 69, 6777 (2003);
[2] Lopes et al., BBA, 1788, 2252 (2009).

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Oligomerization of Huntingtin N-Terminal Fragment on a Phospholipid Bilayer Revealed by Molecular Dynamics Simulations

Sebastien Cote[1], Vincent Binette[1], Evgeniy S. Salnikov[2], Burkhard Bechinger[2], Guanghong Wei[3], Normand Mousseau[1].
[1]Physique, Universite de Montreal, Montreal, QC, Canada, [2]University of Strasbourg, Strasbourg, France, [3]Physics, Fudan University, Shanghai, China.

The Huntingtin protein is characterized by a consecutive segment of glutamines that leads, when the number of repeats exceeds a certain length, to fibrillation. Misfolding of this amyloid protein is related to the Huntington's disease through pathways that could involve interactions with phospholipid membranes. For instance,